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THE DIURETIC ACTION OF ALCOHOL IN MAN[1]

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IT is a matter of common observation that the taking of alcoholic drinks is followed by an increased output of urine. In the case of beer-drinking, this is not surprising, since large volumes are usually consumed; and in the case of some other beverages, e.g. gin, a diuretic agent is present in the drink. The observed diuresis is usually attributed to a combination of these two factors, and most writers either state categorically or imply that alcohol per se has no diuretic action. In 1932, however, from a comparison of the diuretic effects of a given volume of water, with and without alcohol, on two subjects, Murray concluded that alcohol itself was exerting a diuretic action. No alcohol estimations were made, but from observations on the composition of the urine (chloride and phosphate concentrations) and on the inhibitory action of pituitary extract, it was concluded that the mechanism of alcohol diuresis was of the same nature as that of water diuresis.

The diuretic action of alcohol has now been demonstrated on five other subjects, and its mode of action investigated by simultaneous analysis of alcohol concentration in the blood and urine.

METHODS

To each subject the same volume of fluid was given on different occasions; it had a constant basis of cider (70%) to render it more potable and varied only in its alcohol content. Since the experiments were often of long duration and avoidance of fatigue necessary in view of other aspects of the experiment, a light breakfast was allowed (tea or coffee, toast and butter). The dose of alcohol was always given $2\frac{1}{2}$–3 hr. after this, and was usually drunk in the space of 10–15 min. along with

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two or three dry biscuits. The bladder was emptied prior to this, and urine samples collected at frequent intervals. The subjects used appeared to experience no difficulty in attaining complete emptying of the bladder, except occasionally when in an advanced stage of intoxication.

Blood samples were collected from a pin-prick in the bent capillary tubes described by Widmark [1922]. Immersion of the hand in hot water, and use of a sharp glass pricker, ensured a free supply of arterial blood from which 0·1–0·2 g. could be readily obtained. The capillary tube was then weighed on a torsion balance, the blood blown out into a measured 1 c.c. of water in a small vessel, and the empty tube reweighed. By immediate thorough washing, each tube could be used indefinitely; a saturated solution of oxalate was drawn through and the tube then dried by passage of an air current. The dried oxalate weighed not more than 1 mg. and was ignored in the blood weighings, but served to lengthen materially the clotting time of the blood.

The water and blood were well mixed and could be left in safety in the ice chest for analysis the following day, provided the vessels were of such a size that no appreciable air space existed above the fluid. The analysis of blood alcohol concentration was then carried out in the same way as that already described for undiluted plasma [Eggleton, 1940]; 1 c.c. of the diluted blood was used, the distillate received into $N/100$ $K_2Cr_2O_7$ in 50 % H_2SO_4 in place of $N/20$, and the titration carried out with $N/200$ thiosulphate in place of $N/40$. With these dilutions, great attention to detail was necessary at every stage in the proceedings, and a final accuracy of 2–3 mg./100 g. was attained in place of the $\frac{1}{2}$–1 mg./100 g. with the stronger solutions. One source of error was undoubtedly the rubber connexions between the tube of the distilling flask and that of the receiving vessel. A variable error of 0·02–0·04 c.c. $N/40$ thiosulphate ($\frac{1}{2}$–1 mg. alcohol/100 g. blood) from this source passed unnoticed in the original method, but was magnified to 0·1–0·2 c.c. $N/200$ thiosulphate (2–5 mg. alcohol/100 g. blood) with the weaker solutions, and an average blank value of 0·15 c.c. had, therefore, to be subtracted from all titres. Analysis by both macro- and micro-methods of blood to which alcohol had been added indicated that recovery was equally complete in the two, although the variable error was greater in the micro-method.

This method was evolved as an alternative to the Widmark method, since conditions prohibited satisfactory use of the latter. There the titration, with consequent possibility of contamination with tap grease, etc., is carried out in the same flask in which the dichromate solution in concentrated sulphuric acid is kept during the distillation; the flasks, therefore, must be cleaned chemically between each estimation and then thoroughly dried. Without large numbers of the apparatus and a dust-protected room or large cupboard for their sole use, serial blood sampling is impossible. A further disadvantage of such specialized apparatus is the dependence of analytical accuracy on its exact shape. In the dozen apparatus made for me in this country, the small cup which holds the blood was made rather deeper and less wide than that in the original, with the result that complete distillation of the alcohol required 3 hr. instead of 2 hr.

Under suitable conditions, it is likely that the Widmark method might yield more accurate results than the one described above, but in many circumstances the simplicity of the latter would make its use preferable. In any case, the errors involved are small in comparison with those likely to be encountered on the experimental side. Unless free bleeding is induced by the prick (and this is sometimes difficult in subjects with thick skins or in those who do not readily tolerate hot water) and the sample taken quickly into the capillary tube, erratic values are obtained. If the finger is squeezed unduly, plasma may preponderate, leading to artificially high values; and if the blood is not taken quickly, alcohol evaporates from the relatively large surface exposed, and artificially low values are obtained.

Results

Diuresis

Relation to dose of alcohol. In four subjects, two or three different doses of alcohol were given on different days, and the total urine output measured until the resultant diuresis had come to an end, usually in

TABLE 1. The relation between dose of alcohol and degree of diuresis

Subject	Weight kg.	Drink: Volume c.c.	Drink: Alcohol content g.	Total urine output ($2\frac{1}{2}$ hr.) c.c.
H, ♂	70·5	300	8	108
		300	59·5	858
C, ♂	63	300	8	114
		300	52	830
		300	74	1360
A, ♂	60·5	300	8	82
		300	60	642
S, ♀	66	200	26	710
		200	55	1320

2–$2\frac{1}{2}$ hr. The results are presented in Table 1. The only variable factor in the drink was the amount of alcohol, and it is seen that the degree of diuresis in all subjects varied with the dose of alcohol. Under the conditions of these experiments, i.e. a light breakfast 2–$2\frac{1}{2}$ hr. beforehand, all subjects are in water deficit, and respond to the small dose of alcohol (that contained in the cider) by retaining much of the fluid.

In the fifth subject, many more experiments were performed, and the results of these are shown in Fig. 1. There is a considerable scatter of the individual points around the mean, but the general trend is undoubtedly the same. Roughly, every extra 10 g. alcohol results in an extra 100 c.c.

urine excretion. In all of the experiments on this subject, the drink was 200 c.c. in volume (70 % cider) and varied only in its alcohol content. Of the possible factors responsible for the degree of variation indicated in Fig. 1, one was found to be of unexpectedly great importance, namely,

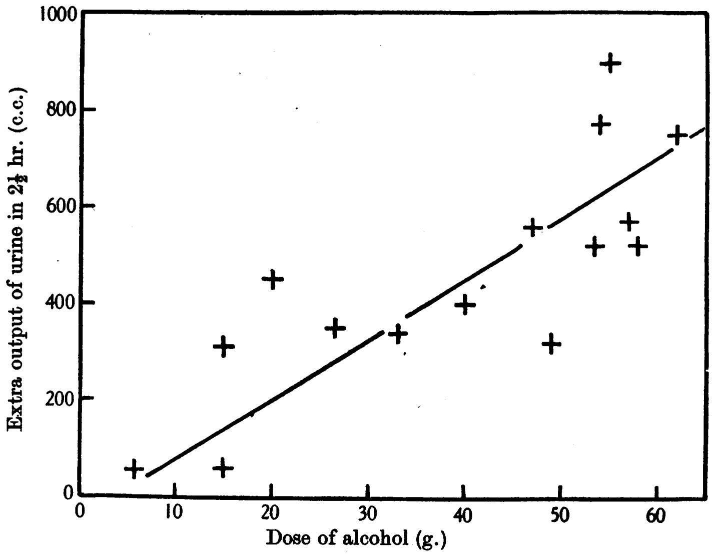

Fig. 1. The relation between dosage of alcohol and diuretic response in one subject when the volume and other constituents of the drink are kept constant.

room temperature. These experiments were carried out during the months of January to July, and although the laboratory was well warmed in winter and on the cool side of the building in regard to summer heat,

TABLE 2. The effect of external temperature on the diuretic response to alcohol in one subject

Dose of alcohol g./kg.	Room temp.	Total urine output (2½ hr.) c.c./g. alcohol/kg. body weight
0·38	Cold	1420
0·28–1·17	Normal	930 ± 105 (10)
0·62	Warm	720
0·28	„	500
0·98	„	430
1·1	Very warm	550
0·92	„	440

there was a considerable variation in temperature throughout the period. No records of this were kept, but only extreme variations noted. Experiments in which this was done are quoted in Table 2. In view of the large differences observed on these occasions, it seems likely that some of the variation amongst experiments in the 'normal' group was also due to unnoted temperature differences. In later sets of experiments, therefore, every effort was made to reduce the variability of this factor.

Time relation to blood-alcohol concentration. It was hoped that further information as to the mechanism of this diuresis might be obtained from a knowledge of the relationship of the course of diuresis to changes in the

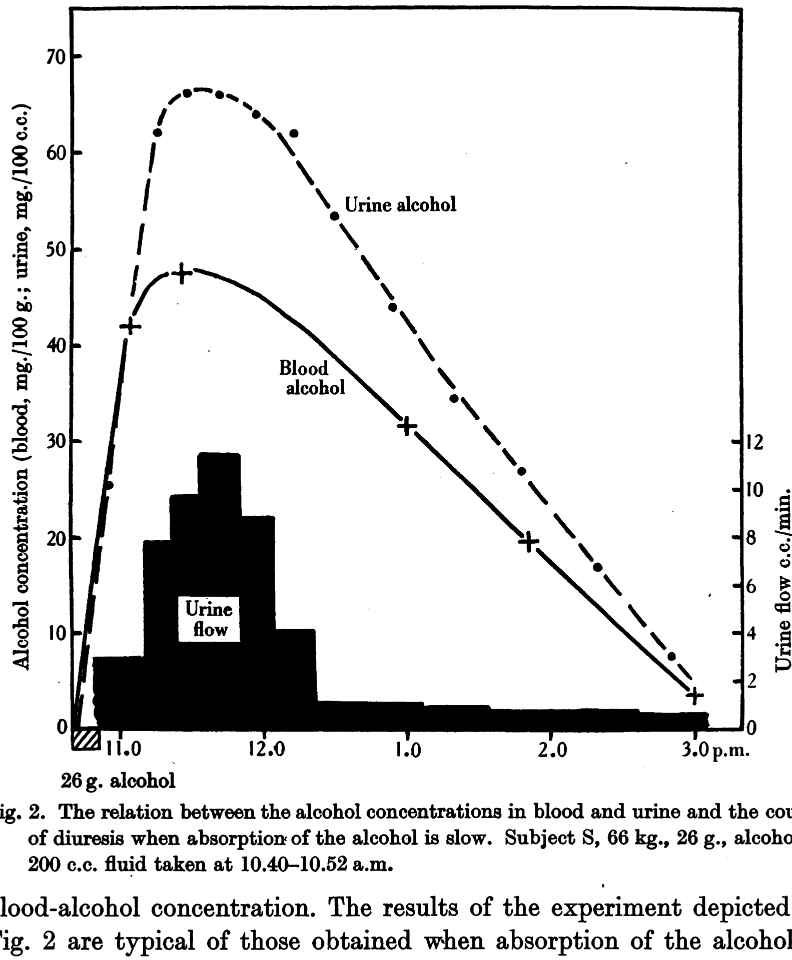

Fig. 2. The relation between the alcohol concentrations in blood and urine and the course of diuresis when absorption of the alcohol is slow. Subject S, 66 kg., 26 g., alcohol in 200 c.c. fluid taken at 10.40–10.52 a.m.

blood-alcohol concentration. The results of the experiment depicted in Fig. 2 are typical of those obtained when absorption of the alcohol is slow. The height of diuresis coincides approximately with the peak value of blood-alcohol concentration. This apparent relationship, however, is a coincidence. If absorption is faster, the blood-alcohol concentration is already decreasing when the height of the diuresis is reached. Such a case is shown in Fig. 3.

The time relationship of diuresis to blood-alcohol concentration suggests that this relationship may be of hormonal nature, as suggested

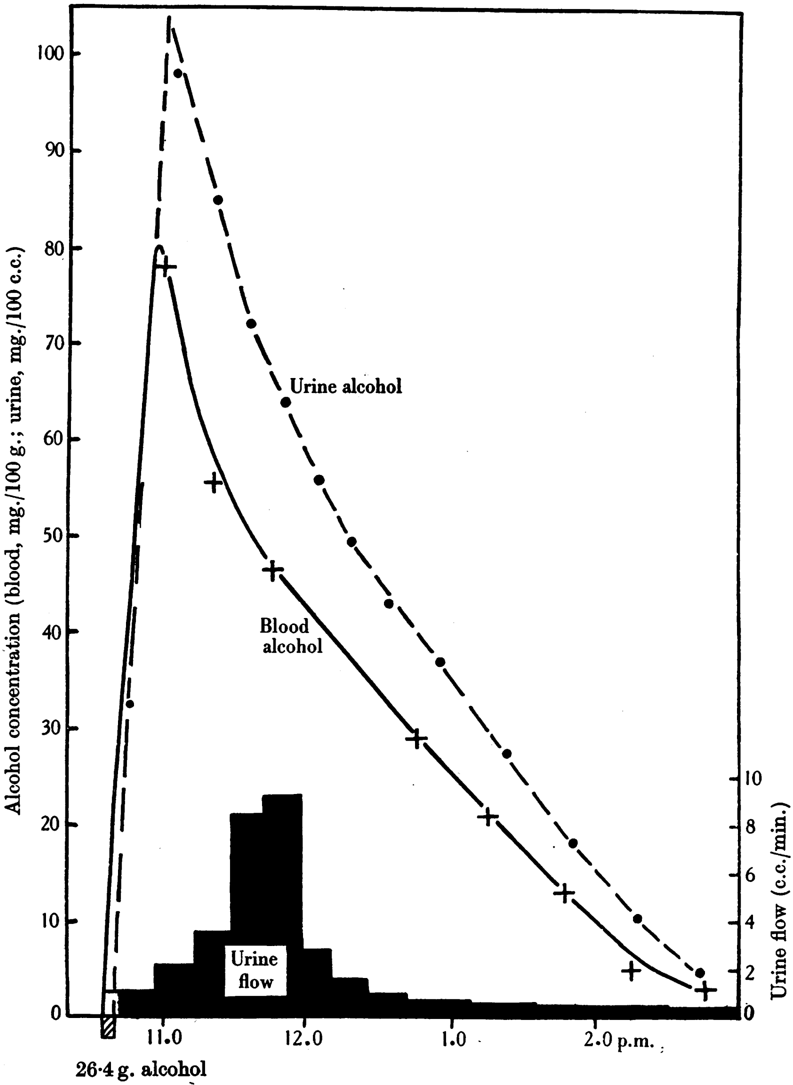

Fig. 3. The relation between alcohol concentrations in blood and urine and the course of diuresis when absorption is rapid. Subject E, 52·5 kg., 26·4 g. alcohol in 200 c.c. taken at 10.35–10.40 a.m.

by Murray [1932]. Her results have been amply confirmed; post-pituitary extract will completely inhibit alcohol diuresis, although this form of diuresis appears to be somewhat more resistant to its action than is a water diuresis. On the first occasion, 1 unit was injected 15 min. before the alcohol was taken. The onset of diuresis was delayed until 1½ hr. after the alcohol had been taken, and then amounted to 450 c.c. instead of the

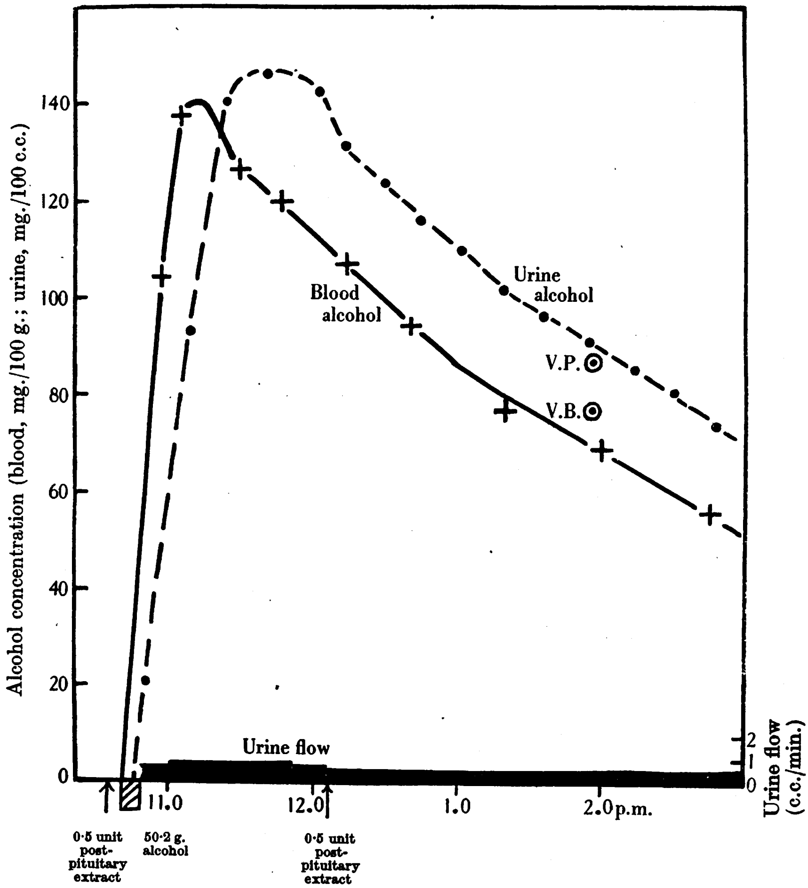

Fig. 4. The effect of post-pituitary extract in suppressing the diuretic response to alcohol. Subject E, 52·5 kg. *V.P.* and *V.B.* = alcohol concentration (mg./100 c.c.) in venous plasma and blood respectively.

600–800 c.c. expected after a dose of 50 g. alcohol. In a second case, 0·5 unit was injected 5 min. before a dose of 50 g. alcohol and another 0·5 unit 1¼ hr. later (Fig. 4). In a third case, 1 unit was given 3 min. before 53·5 g. alcohol and another unit 1½ hr. later. In both of these experiments diuresis was completely absent (see Fig. 4). These results, taken in conjunction with the fact that the normal alcohol diuresis shows the same lag in onset as a water diuresis is very suggestive that the same mechanism is responsible for both.

If this is the case, the question still remains as to whether the pituitary gland is inhibited directly, or by way of its nervous control in the hypothalamus. The latter would seem more probable in view of the depressant

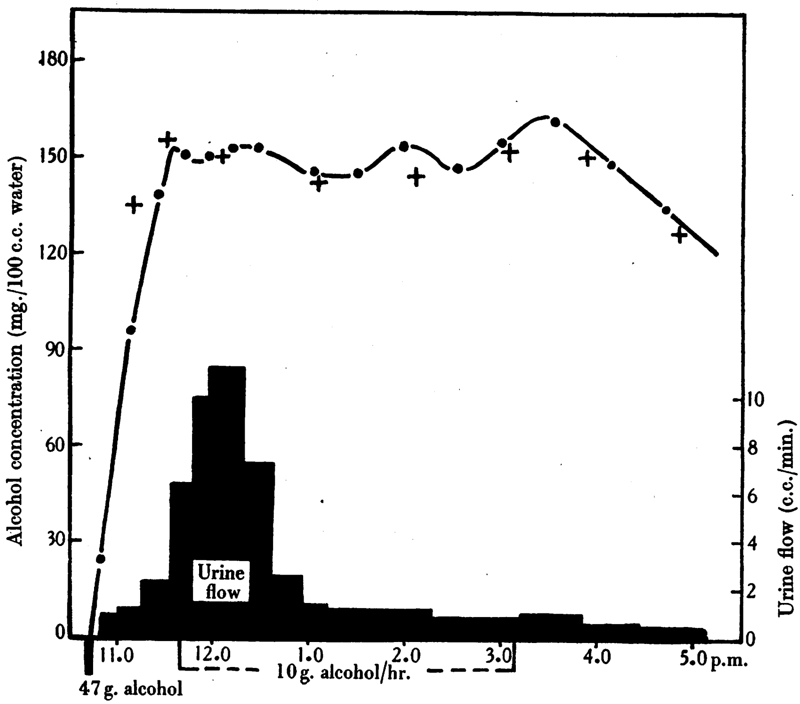

Fig. 5. The effect of a steady concentration of blood-alcohol in failing to maintain diuresis. Subject E, 53 kg., 47 g. alcohol in 200 c.c. taken at 10.40–10.50 a.m. From 11.40 a.m. to 3.10 p.m. 38·3 g. in 233 c.c. taken in 20 c.c. doses every 20 min. ●——● = urine alcohol; + = blood alcohol (concentration in mg./100 c.c. water).

action of alcohol on other parts of the central nervous system, but there are some difficulties which prevent a ready acceptance of this theory. Concerning the action of alcohol on cortical function, as reflected in sensori-motor and other tests, it has been shown that although the absolute concentration of alcohol is a potent factor in the depressant action, the rate and direction of its change may be equally important: at any given concentration, greater effect is produced if it is increasing than if it is decreasing, and this effect also varies directly with the rate of increase [Eggleton, 1941]. Evidence to be now presented suggests that these statements cannot be fully applied to the diuretic action.

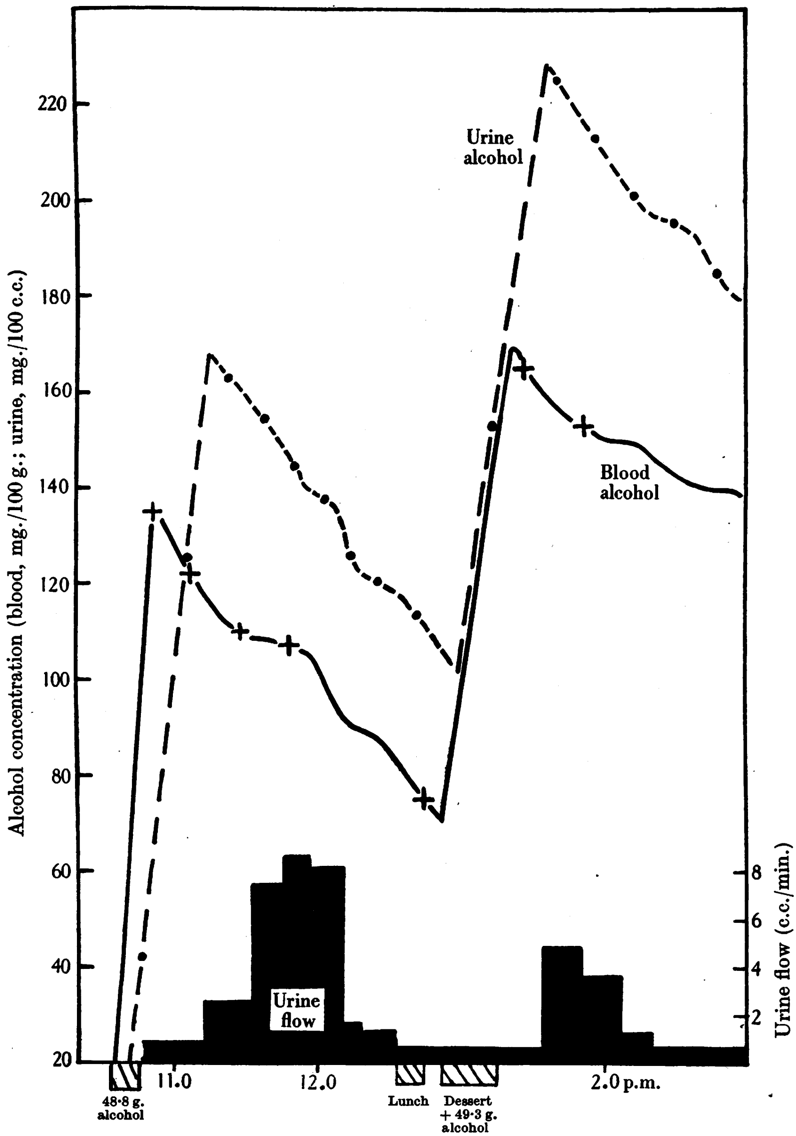

Fig. 6. The diuretic action of a second increase in blood-alcohol concentration following the subsidence of a first response. Subject E, 52·5 kg.

Effect of increasing blood-alcohol concentration. The *increase* in blood-alcohol concentration appears to be the main factor in producing the diuresis. When this change ceases, even although the absolute concentration is maintained, the diuresis ceases just as abruptly as if only a single dose of alcohol had been given. Such a result is shown in Fig. 5. The diuresis following a dose of 47 g. is of average size (700 c.c.) and duration ($2\frac{1}{2}$ hr.), although the blood-alcohol concentration was maintained at 105–115 mg./100 g. (140–150 mg./100 g. water) for 4 hr. The cessation of diuresis cannot be attributed to dehydration of the body because a second single dose of alcohol given after the diuretic response to the first has died away, will initiate a second period of diuresis. Such a result is shown in Fig. 6. The second response is not so large as the first, 210 c.c. in place of 410 c.c., but antagonizing factors were many: the body was in water deficit from the first diuresis, the room temperature was unusually high (noted as a very warm day), and food had been taken, withdrawing fluid into the stomach and intestines. In spite of all these dehydrating factors, the second increase in blood-alcohol concentration initiated a diuresis.

Effect of duration of increasing blood-alcohol concentration. The effective action of an increasing blood-alcohol concentration is thus common to both cortical function and diuretic response. If the latter is initiated through a nervous mechanism, it might be expected that it also would respond to *rate of increase* in blood-alcohol concentration in the same manner as does the cortex, and that the two types of response would vary in the same direction. Cortical function is most disturbed by a fast rate of increase in alcohol concentration, but it became clear during the course of these experiments that no such direct relationship existed in the case of the diuretic response.

Comparison of Figs. 2 and 3 suggests that the duration of the stimulus is a more important factor than the actual rate of increase or absolute concentration of alcohol. In subject S (Fig. 2) a diuresis of 710 c.c. resulted from a blood-alcohol concentration of only 48 mg./100 g. reached in 50–60 min., whereas subject E (Fig. 3) gave a response of only 440 c.c. to a blood-alcohol concentration of 80 mg./100 g. reached in 20–30 min. Thus the larger diuresis accompanied the slower rate of increase in blood-alcohol concentration and vice versa. The variation in diuretic response of five subjects listed in Table 1 and Fig. 1 tended in the same direction. This variation can be more easily appreciated from the figures in Table 3, where the diuresis is expressed in terms of a standard dose of alcohol, 1 g./kg. body weight. It would seem that the mechanism responsible for this diuresis is more than twice as sensitive in some individuals as in others, and that this variation may be partially due to variations in the duration of the

TABLE 3. A comparison of the degree of diuresis in different individuals to the same dose of alcohol

Subject	Total urine output ($2\frac{1}{2}$ hr.) c.c./g. alcohol/kg. body weight
S, ♀	1690 ± 110 (2)
H, ♂	1035 ± 85 (2)
C, ♂	1020 ± 80 (2)
E, ♀	835 ± 90 (16)
A, ♂	635 ± 15 (2)

increase in blood-alcohol concentration, for subject S was on all occasions the slowest absorber and subjects A and E the fastest.

The general impression gained from experiments on these five subjects was reinforced by results from further experiments on a second series of seven other subjects. Blood-alcohol determinations were no longer feasible owing to enemy action, but experience has shown that the course, though not the absolute value, of blood alcohol concentration can be fairly accurately judged from tests of cortical function [Eggleton, 1941]. The degree of upset of the nervous system reflected in these tests is greater if the blood-alcohol concentration increases more rapidly, greatest at the peak value, and decreases rapidly with decrease in alcohol concentration. The group of seven subjects, therefore, became well practised on the dotting machine, and a comparison was then made of

TABLE 4. Relative effects of the duration and intensity of alcohol action on the diuretic response

			Dotting machine performance maximum error		
Exp.	Subject	Weight kg.	% decrease in correct hits	Time after beginning of drink min.	Total urine output in $2\frac{1}{2}$ hr.
1	R. A. B. ♂	90	19·5	26	240
2	D. R. W. ♂	54	17·5	37	445
3*	D. I. H. ♀	55	>36	<32	520
4	P. L. L. ♂	66	10	67	530
			8	107	
5	D. R. W. ♂	54	18	40	680
			22	107	
6	D. F. R. ♂	58	29	16	720
			21	34	
7	J. D. ♀	64	33	15	930
			30	30	
8	J. D. ♀	64	24	40	1080
			12	100	

A dose of 45 g. alcohol in 250 c.c. was given to all subjects.

* Owing to a misunderstanding, the first test was not made until the subject was already beginning to recover, subjectively.

the effect of a standard dose of alcohol (45 g. in 250 c.c., water only) on their dotting performance and diuretic response. The results are presented in Table 4, in ascending order of diuretic response. Apart from the first subject listed, this response is unconnected with body weight. The general trend of the results supports the impression gained from the earlier subjects, that the duration of alcohol action, rather than a short, swift effect, is the potent factor in determining the extent of the diuresis. The occurrence of more than one peak value, due no doubt to irregular emptying of the stomach, indicates that the nervous system was subjected to more than one period of increasing blood-alcohol concentration.

Cause of individual variation in diuretic response. A closer survey of these results suggests that some individual personal factor may be also partially responsible for the large variation in diuresis observed. A comparison of Exps. 5 and 8, for example, shows a wide variation in diuretic response in two individuals (680 and 1080 c.c. respectively) with approximately the same rate of absorption and degree of nervous upset. The possibility that this degree of variation might be due to individual variation in sensitivity of the pituitary mechanism, if this hypothesis of the diuretic action be accepted, is an obvious one. An attempt was next made, therefore, to see whether such a variation might be responsible. In a further group of subjects, the diuretic response to both alcohol and water was studied. Both substances were given roughly in proportion to the body surface, i.e. to the weight[‡]: a 60 kg. man receiving 38·5 g. alcohol in 200 c.c. (water only) and 1 l. of water. A wide range of response was encountered, both in dotting performance and in the two types of diuresis. The percentage decrease in correct hits in the dotting test varied from 1 or 2 % to over 40 %, and individual variation in both alcohol and water diuresis was nearly 100 %. The degree of upset of the nervous system was assessed in arbitrary units, equal weight being given to intensity and duration; thus, one unit represented 10 % decrease in correct hits in the dotting test for 10 min., or 5 % for 20 min., etc. The scores ranged from 0 to 40, but no correlation was observed between this value and the diuretic response to alcohol. Nor was any correlation of statistical significance, either positive or negative, found between water and alcohol diuresis. The complexity of factors concerned masked any such simple correlation, and the only relationship which could be established is that indicated in Table 5.

Initially, there were fifteen subjects, but three felt ill as a result of the alcohol, and the resulting autonomic disturbance stopped the renal flow; in one the water diuresis was prolonged over many hours, presumably due to delayed emptying of the stomach; and in

TABLE 5. Effect of duration of alcohol action on the relation between water and alcohol diuresis

Exp.	Subject	Peak time* of alcohol absorption min.	Diuresis (arbitrary units)† Alcohol	Water	Ratio water/alcohol
1	R. E. M. ♂	15–20	22	49	2·2
2	D. M. E. ♂	25	21·5	43	2·0
3	C. F. R. ♂	25	19	32	1·7
			21 ± 1	41 ± 5	
4	S. W. S. ♂	25 and 55	19·5	33	1·7
5	J. D. ♀	30 and 50	23·5	38·5	1·65
6	J. P. ♀	45	28·5	43·5	1·5
7	M. H. ♀	45	23	32	1·4
8	R. C. ♀	50	29	35·5	1·2
9	R. J. ♀	20, 60 and 120	21	27	1·3
10	P. L. L. ♂	80 and 135	28	30·5	1·1
			$24·5 \pm 1·5$	34 ± 2	

* Assessed from time of worst performance on dotting machine.

† Volume excreted in relation to body weight: 1000 c.c. in 60 kg. man = 30 units. Volumes imbibed: water 30; alcohol solution 6.

another, this failure to empty the stomach occurred after alcohol, so that neither diuresis nor upset of the central nervous system was observed. This case is discussed more fully later. In all subjects, the previous meal had been omitted, either breakfast or lunch; the body was in approximate water balance, since two glasses of water were taken 2–2½ hr. before each experiment; and the alcohol and water, or water and alcohol, experiments were performed on successive days at the same time of day. By alternating the order in which the two experiments were done, the effect of changes in temperature were largely annulled. In the second part of Table 5 two values should be increased and two decreased, owing to this factor. In the first part of the Table, the lowest ratio, 1·7, should be increased.

The results have been arranged approximately in order of increasing duration of alcohol action, and subdivided into a group of three rapid absorbers and the remaining seven slower ones. The alcohol diuresis is slightly smaller in the former group than in the latter, but the difference is barely significant. The reverse is the case in respect of water diuresis, but again there is no significant difference. This tendency to a negative correlation between alcohol and water diureses might be expected if the rate of emptying of the stomach was a constant factor in any individual; rapid absorption of water is likely to produce a greater diuresis than does slow absorption, whereas rapid absorption of alcohol, with short duration of its action, appears to produce a smaller diuresis than does slow absorption.

If rapidity of absorption, both of alcohol and of water, was the only factor concerned in the diuretic response, a more orderly arrangement of increasing alcohol diuresis and decreasing water diuresis in relation to the duration of alcohol action (as indicative of the natural rate of emptying of the stomach) might have been expected. If some further individual factor is concerned, conditioning the magnitude of the diuretic response in both cases, its effect might become apparent if the ratio of the two diureses were considered. These figures are shown in the last column of the table, and do in fact show a much more orderly sequence. A comparison of subjects 6 and 7, in whom this ratio was approximately the same, will illustrate the point in question. Both absorbed alcohol at the same rate and both showed only a slight disturbance of cortical function, but in subject 6 the diuresis was considerably greater than in subject 7. The fact that subject 6 showed also a much larger diuretic response to water (although the two water diuresis experiments were done on the same day) suggests that the mechanism concerned in both responses was more sensitive than in subject 7.

The variation in ratio, ranging from 2·2 to 1·1 in different individuals, is an expression of the opposite effects of the rate of absorption on alcohol diuresis on the one hand and water diuresis on the other. The orderly nature of the change, however, is strongly suggestive of the presence of another factor, tentatively referred to as 'sensitivity of the pituitary mechanism', which varies in different individuals. With the evidence available, this can be no more than a suggestion, and must await confirmation or the reverse from experiments under much more carefully controlled conditions.

Relative importance of the different factors concerned. In view of this result, the clearest evidence of relationship between duration and intensity of alcohol action on the diuretic response should be obtainable by varying these factors in experiments on one individual, in whom the 'sensitivity of the pituitary mechanism' may be accepted as approximately constant. Comparisons of some earlier experiments on one subject (E), in which blood-alcohol concentration was estimated directly, have been grouped in Table 6. In the first couple it is seen that long duration of stimulus (obtained by sipping the drink over a long time), and lower absolute concentration of alcohol, produce less depression of the cortex but greater diuresis than a short but more intense stimulus. In the second couple, the same absolute value of blood-alcohol concentration was reached, but again the longer-lasting stimulus produced a smaller cortical and larger diuretic effect than the shorter stimulus.

A modification of these experiments has been repeated on the same subject, without analysis of the blood-alcohol concentration. The same dose of alcohol was given on several occasions under identical conditions as far as possible, but with varying rates of absorption. The results

TABLE 6. Effect of duration and intensity factors in the action of alcohol on the central nervous system and on the diuretic response

Dose of alcohol g.	Blood-alcohol concentration: Peak value mg./100 g.	Blood-alcohol concentration: Time taken to reach peak min.	C.N.S. effect % increase in: Typing time errors	C.N.S. effect % increase in: Distraction machine errors*	Diuresis c.c./2½ hr.
40	135	20	—	70	480
52	118	90	—	20	540
56	155	45	90	—	710
62	152	72	45	—	965

All experiments performed on the same subject (52 kg.), and the volume of drink kept constant (200 c.c.).

* Details of tests given elsewhere [Eggleton, 1941].

tabulated below (Table 7) show unmistakably that the degree of alcohol diuresis is connected with the duration of the rising blood-alcohol concentration and not with the intensity of its effect on the higher nervous system. Although the general trend of these results is so definite, their

TABLE 7. Effect of duration of alcohol action on the central nervous system and on the diuretic response

Peak time* of alcohol absorption min.	Dotting machine total time errors†	Diuresis c.c./2½ hr.
10	11	455
10 and 35	38	490
5 and 50	21	630
90	0	670
90	0	770

The same dose of alcohol (35 g. in 180 c.c.) taken in all experiments by the same subject (52 kg.).

* Assessed from time of worst performance on dotting machine in Exps. 1 to 3, and from duration of drinking time in 4 and 5.

† 1 unit = 10% decrease in performance for 10 min., 5% decrease for 20 min., etc.

regularity is not as great as might have been expected. Certain interfering factors, though uncontrollable, were recognized at the time. The third value, 630 c.c., was obtained on a 'very cold' day in contrast with the remaining values all obtained on 'fairly cold' days, and was, therefore, unduly large. The next value, 670 c.c., probably represented an absorption time of about 70 min. in place of the expected 90 min., owing to a failure of the stomach to empty during the early period of drinking. Although no signs of central nervous system disturbance could be detected by means of the dotting machine, either in this or in the last experiment, euphoria was noticed in both; it was first recorded 20 min. after the beginning of the drink in the last experiment, but not until 40 min. after in the previous one. It would seem that more accurately quantitative results cannot be obtained on man unless the alcohol be given by duodenal tube or intravenously, and the experiments carried out in a room at constant temperature.

Clearly, there must be some limiting rate of increase in blood-alcohol concentration to which the diuretic mechanism is no longer responsive, but under the conditions employed in these experiments it was not deliberately reached. In one subject mentioned in the previous section, this state of affairs was encountered. Neither diuresis nor any effect on the central nervous system occurred after the usual dose of alcohol. An attempt was made subsequently to hasten emptying of the stomach by giving magnesia tablets with the drink, on the advice of a friend given from empirical observation of its effect. A small diuretic response was obtained (14 in arbitrary units), but results on the dotting machine indicated a very erratic behaviour of the pylorus, and the result has not been included in Table 5. His water diuresis figure was 27, one of the lowest observed.

The action of magnesia was again tested in the first experiment quoted in Table 7. The whole drink (35 g. alcohol in 180 c.c.) was taken in 5 min. with two magnesia tablets and the usual two dry biscuits. The stomach began to empty rapidly, as evidenced by a dotting score of 28 % decrease in correct hits 10 min. after the beginning of the drink. The nervous system then made a smooth recovery and no further upset was observed during the 2½ hr. of experiment. The total time-errors score was very much smaller than would have been the case if any large fraction of the dose had left the stomach at this early stage, and the results suggest that the remainder left so slowly that it had no further effect either on the nervous system or in promoting diuresis. It seems likely that the same phenomenon was responsible for the small diuresis of subject D. R. W. in Exp. 2 of Table 4. The dose given produced a much larger effect both on the nervous system and on the diuretic response in a subsequent experiment (5).

The actual rate of increase in blood-alcohol concentration responsible for the larger diureses shown in Table 7 can be calculated approximately. In the 90 min. of absorption at least one-third of the 35 g. ingested would have been metabolized (the average rate of metabolism in this subject was 8–10 g./hr.), and the remaining 22 g. be distributed in about 36 kg. of tissue (body weight 52 kg. × 0·7), yielding a blood-alcohol concentration of *ca.* 60 mg./100 g. Thus the rate of increase in concentration during the 90 min. would be *ca.* 0·7 mg./100 g./min.

Discussion and conclusions

The evidence presented indicates that, under comparable conditions, the diuresis initiated by alcohol in any individual varies directly with the quantity taken. This relationship is disturbed (*a*) by variations in external temperature, due presumably to greater loss of fluid in sweat under hot conditions, and (*b*) by variations in the rate of absorption of alcohol. If this be slowed in the naturally fast absorber, a larger diuresis results from the same dose of alcohol.

When the response of different individuals to the same dose of alcohol (given in relation to body weight or body surface) is compared, a large variation in diuretic response is encountered. This variation appears to be due primarily to differing rates of absorption, the naturally slow absorber (due presumably to slow emptying of the stomach) responding with a larger diuresis than the naturally fast absorber. This relationship, however, is not consistently observed when the responses of groups of individuals are compared, but is obscured by some further individual variable factor.

The evidence presented as to the nature of this second variable factor is not conclusive, but suggests that it may be linked with individual variation in diuretic response to water. In the first place, an alcohol diuresis can be inhibited by post-pituitary extract in the same order of dose, as can a water diuresis, and this may be accepted as presumptive evidence that the same mechanism is concerned in the initiation of the two types of diuresis. Secondly, the naturally rapid absorber appears to give a larger diuretic response to water than does the naturally slow absorber. When due allowance is made for this opposing combination of effects, however, i.e. large water diuresis and small alcohol diuresis with rapid absorption, a further complementary relationship between the two is revealed, indicative of a natural variation in degree of diuretic response to both stimuli, water and alcohol. This is referred to tentatively as a 'natural variation in sensitivity of the pituitary mechanism'.

The further question as to whether alcohol diuresis is produced by the action of this substance on hypothalamic nerve centres or directly on the pituitary body must remain an open one at present. If the nerve centres are concerned, they differ markedly from the cortex in being more sensitive to duration of increasing blood-alcohol concentration than to its rate of increase.

The relation of alcohol concentration in blood to that in urine

It is generally recognized that alcohol concentration in the urine provides a rough guide to that in the blood, though little quantitative work has been done on this relationship since the classic research of Miles [1922]. He concluded that: 'The alcohol concentration in venous blood and in urine is not identical and does not run parallel in the first two hours after ingestion...still the urine-alcohol curve is very useful for comparison with the time relations of the objective measurements of alcohol effect on the central nervous system.' No micro-method for blood analysis was available at that time, nor was the macro-method in use so accurate as that now available. Under modern conditions of analysis, it is clear from the data already presented (Figs. 2–5) that an accurate reflexion of changes in blood-alcohol concentration can be obtained from analysis of urine samples, provided the changes involved are not too rapid.

Frequent urine sampling is essential, especially when the rate of flow is changing rapidly. Thus, in Fig. 2 the first urine sample was secreted mainly in the second half of the collection period, and the analytical point should, therefore, be moved to the right of the mid-point of this period. Similarly, the sixth sample was secreted mainly in the first half of the sampling period, and its analytical point should be shifted to the left. The actual concentration in the urine is independent of the rate of urine flow as is well known, and the relationship between blood and urine-alcohol concentrations shown in Fig. 4 where diuresis was completely inhibited by pituitrin, is different from that shown in other figures only in respect of the lag of urine-alcohol concentration during the period of rapid change. This is undoubtedly an artefact, due to the small volume of each sample (10–15 c.c.), of which an appreciable proportion must represent a 'wash-out' of the previous sample. During later stages, when alcohol concentration is changing relatively slowly, such frequent sampling is no longer necessary and the effect of this error, therefore, is much less pronounced.

In the slowly changing curves of Fig. 2, the urine-alcohol concentration follows closely the blood-alcohol concentration, at a value 30–35 % higher, except in the early stages of absorption. With swifter absorption, the urine curve lags appreciably behind the blood-alcohol curve on its upward course, and the same lag is often observed when rapid changes occur on the down curve. It seems probable that the explanation given above accounts also for these discrepancies. The rapid changes of concentration in both directions occur only in the rapid absorber, and therefore at a time when urine samples are still small in volume owing to the lag in onset of diuresis. In view of the fact that the urine-alcohol concentration is independent of diuresis, the probability is high that free diffusion of this substance occurs between tubule fluid, renal cells, tissue fluid and blood throughout the substance of the kidney.

In all of the figures it can be seen that the urine-alcohol concentration is 30–35 % higher than blood-alcohol concentration except during the periods of rapid change. The question arises as to whether this difference is compatible with the assumption that the alcohol in urine is in equilibrium with that in the plasma. In the experiment depicted in Fig. 4, a venous sample was taken at one point, enabling analysis by the more accurate macro-method of both blood and plasma. This was repeated in a second experiment, and the results of the two in conjunction with those of the micro-analysis of arterial blood and macro-analysis of urine are presented in Table 8. The ratio of plasma alcohol/blood alcohol, 1·13–1·16,

TABLE 8. The relation of alcohol concentration in urine to that in blood

Alcohol concentration in arterial blood mg./100 g.	Alcohol concentration in venous: Blood mg./100 c.c.	Alcohol concentration in venous: Plasma mg./100 c.c.	Alcohol concentration in urine mg./100 c.c.
71	77	87	91·5
66	69·5	80·5	87·5

Alcohol concentration (mg./100 c.c.) in water of: Arterial blood	Venous blood	Venous plasma	Urine
94	96·5	97	95·5
87	87	89·5	91

agrees with results obtained by Miles. In the second part of the table, the analytical figures have been recalculated in terms of alcohol concentration in the water of each fluid, using the average figures of 80 % in blood, 90 % in plasma and 96 % in urine. The difference between venous and arterial blood is satisfactorily accounted for by the fact that the former was measured by volume and the latter by weight (blood specific gravity, 1·06).

Within the limits of experimental error, including possible deviations from the average in the water content of the various fluids, it is seen that alcohol concentration is the same in the water of blood, plasma and urine. This conclusion is reinforced by the results shown in Fig. 5, in which all analytical figures are expressed in terms of alcohol concentration in the water of blood and urine. It would, therefore, seem justifiable to conclude that urine-alcohol concentration represents alcohol concentration in the tissue fluids, and is practically the same as that in the water of plasma except when rapid changes in concentration are occurring.

SUMMARY

1. A method is described for the estimation of alcohol in blood obtained by pin prick (0·1–0·2 g.). No specialized apparatus is required. Recovery is quantitative, with a variable error of 2–3 mg./100 g.

2. The diuresis following an alcoholic drink is roughly proportional to the amount of alcohol present, when volume and other constituents

are maintained constant (Table 1, Fig. 1). Variations in external temperature may seriously affect this relationship (Table 2).

3. Its onset is delayed for 20–30 min. after the drink has been taken, and the height of diuresis is unrelated in time to the peak of blood-alcohol concentration (Figs. 2, 3).

4. The diuresis can be completely inhibited by post-pituitary extract (Fig. 4).

5. It is initiated by the *increase* in blood-alcohol concentration and fails to be maintained if this concentration is kept steady, even at a high level (Figs. 5, 6).

6. The degree of diuresis resulting from a given dose of alcohol varies widely in different subjects (Table 3).

7. This individual variation is dependent on the natural rate of absorption of alcohol (Table 4) and possibly on a variation in the sensitivity of the pituitary mechanism, as evidenced by variation in the diuretic response to water (Table 5). This variation also appears to be due, in part, to varying rates of absorption of water.

8. The diuretic response to alcohol differs markedly in one respect from that of the cerebral cortex. The latter is most affected by the *rate* of increase in blood-alcohol concentration: the greater this rate of increase, the greater the disturbance of function at any absolute concentration. The diuretic response, on the other hand, is dependent mainly on the *duration* of increasing blood-alcohol concentration and not on the rate of increase (Tables 6, 7). The naturally slow absorber, therefore, tends to give a larger diuretic response than the rapid absorber.

9. When equilibrium has been established in the body, alcohol concentration in the urine remains 30–35 % higher than that in the blood. Comparison of these values with those of arterial blood, and venous blood and plasma indicate that the alcohol in urine is in equilibrium with that in the water of plasma (Figs. 4, 5, Table 8).

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